Pharmacological Reports
2013, 65, 891–897
ISSN 1734-1140

Disparate effects of anti-TNF-α therapies on measures of disease activity and mediators of endothelial damage in ankylosing spondylitis

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Abstract:

Background: Asymmetric dimethylarginine (ADMA) is associated with endothelial injury. Increased ADMA levels are found in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). We set out to assess the ADMA and symmetric dimethylarginine (SDMA) levels in AS, RA, and healthy controls, and in the anti-TNF treated patients with active AS.

Methods: In 78 AS patients and 29 RA patients who were anti-TNF treatment naive at baseline, along with 23 healthy control subjects, we assessed erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), ADMA, and SDMA. For AS patients, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), back pain VAS and patient's global activity of disease were calculated. After 6 months, we repeated the assessment in 30 out of the 78 AS patients in whom the anti-TNF treatment was initiated.

Results: The baseline mean (SD) plasma ADMA concentration of AS patients was 0.64 (0.19) μmol/l and did not differ from controls (0.65 [0.19] μmol/l, $p > 0.05$). In the RA group, ADMA concentration was higher than in controls (0.77 *vs.* 0.65 μmol/l, $p < 0.05$). Both at baseline and at follow-up, ADMA levels correlated positively with BASDAI ($R = 0.52$, $p = 0.02$, and $R = 0.47$, $p = 0.04$, baseline and follow-up, respectively). Six months of anti-TNF treatment did not influence ADMA concentration (0.51 [0.12] *vs.* 0.51 [0.11] μmol/l, $p = 0.70$).

Conclusion: An absence of changes in plasma ADMA levels in the anti-TNF treated AS group despite the improvement in disease activity (BASDAI) and inflammation (ESR, CRP) may suggest either a lack of effect, or, even if such an effect were to take place, it needs not imply measurable changes in blood ADMA.

Key words:
ankylosing spondylitis, endothelium, ADMA, SDMA, TNF inhibitor

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Introduction

Ankylosing spondylitis (AS), affects approximately 1% of the general population. It is a chronic arthritis characterized by inflammation, which leads primarily to remodelling of the axial skeleton [5, 6]. Patients with AS have increased cardiovascular (CV) risk, which is largely responsible for a 2-fold increase in mortality compared with the general population [17, 21]. Accelerated atherosclerosis significantly contributes to CV risk [12] and may be induced both by traditional CV risk factors (e.g., hyperlipidemia) [30] and inflammation itself [7]. Endothelial dysfunction, which initiates atherosclerosis, is a predictor of long-term CV risk [32].

Asymmetric dimethylarginine (ADMA) is the endogenous inhibitor of nitric oxide (NO) synthase and increased levels of this molecule are responsible for reduced NO synthesis and endothelium damage [2]. ADMA acts directly on the enzyme NO synthase, while its analogue, symmetric dimethylarginine (SDMA), is thought to be important as a competitive inhibitor for arginine transport across cell membranes [18]. Elevated plasma concentrations of ADMA have been shown to accompany a number of traditional CV risk factors, i.e., hyperlipidemia, hypertension, diabetes mellitus, insulin resistance and smoking. Increased ADMA levels are responsible for endothelial injury and the progression of atherosclerosis and have been found to be an independent predictor of CV morbidity and mortality [3]. It has been demonstrated that ADMA is elevated in various inflammatory diseases, including systemic lupus erythematosus, systemic sclerosis, Behcet disease, familial Mediterranean fever and rheumatoid arthritis [25]. Recently, ADMA levels have been found to be significantly increased in AS patients as compared with healthy controls [9, 23] and patients with osteoarthritis (OA) [16].

Tumor necrosis factor- (TNF-) α is a pivotal proinflammatory cytokine in AS [8] and may be responsible for the pathogenesis of endothelial damage in chronic inflammatory disease, i.e., rheumatoid arthritis [10, 13]. Anti-TNF-α treatment has been shown to improve the disease course and outcome in AS. One study suggested that anti-TNF-α treatment might decrease levels of circulating ADMA in patients with relatively early AS free from traditional CV risk factors [23]. Two further studies revealed that anti-TNF-α treatment does not influence ADMA levels [9, 16], which were found to be similar in TNF inhibitor treated and untreated AS groups.

The aim of the present study was to evaluate the plasma level of ADMA and SDMA in AS, RA and controls, and further, the effect of TNF inhibition on ADMA and SDMA levels in a group of AS patients with high disease activity.

Patients and Methods

The study population comprised 130 individuals, recruited in three centres. Included in the study were 78 consecutive AS patients, 29 RA patients and 23 healthy individuals for cross-sectional analysis; 30 out of 78 AS patients were then used for longitudinal investigation.

Ankylosing spondylitis patients were TNF inhibitor and synthetic disease modifying anti-rheumatic drugs (DMARDs) naive and were diagnosed with AS according to the modified New York criteria [29]. Thirty AS patients with high disease activity were assigned to TNF inhibitor therapy and analyzed longitudinally. Patients were considered as having high disease activity if the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was ≥ 4, the patient's back pain visual analogue scale (VAS) was ≥ 4 cm, the patient's global activity of disease was > 5 cm and if they were refractory to at least two NSAIDs. Twenty-three active AS patients received etanercept and 7 adalimumab, according to the manufacturers' respective dosing schedules. All patients used NSAIDs throughout the study. Forty eight AS control patients who were not eligible for anti-TNF treatment were treated with NSAIDs only. All AS patients had an axial disease, and 21.8% had peripheral signs; 96.1% of patients were HLA-B27 positive. Twenty-nine RA patients with early disease fulfilling 1987 American College of Rheumatology revised criteria [1] were anti-TNF and synthetic DMARDs naive and were treated with NSAIDs and/or steroids. Uncontrolled arterial hypertension, diabetes mellitus, premature coronary artery disease (< 55 years in men and < 65 years in women), previous cardiovascular, cerebrovascular or peripheral arterial events, hyperlipidemia and statin use were the exclusion criteria. A total of 23 healthy volunteers (11 males) who were also subject to the exclusion criteria listed above served as controls. Current smoking levels were recorded for all patients and controls.